Deregulation of HMGA1 expression induces chromosome instability through regulation of spindle assembly checkpoint genes.

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Abstract

The mitotic spindle assembly checkpoint (SAC) is an essential control system of the cell cycle that contributes to mantain the genomic stability of eukaryotic cells. SAC genes expression is often deregulated in cancer cells, leading to checkpoint impairment and chromosome instability. The mechanisms responsible for the transcriptional regulation and deregulation of these genes are still largely unknown. Herein we identify the nonhistone architectural nuclear proteins High Mobility Group A1 (HMGA1), whose overexpression is a feature of several human malignancies and has a key role in cancer progression, as transcriptional regulators of SAC genes expression. In particular, we show that HMGA1 proteins are able to increase the expression of the SAC genes Ttk, Mad2l1, Bub1 and Bub1b, binding to their promoter regions. Consistently, HMGA1-depletion induces SAC genes downregulation associated to several mitotic defects. In particular, we observed a high number of unaligned chromosomes in metaphase, a reduction of prometaphase time, a delay of anaphase, a higher cytokinesis time and a higher percentage of cytokinesis failure by using live-cell microscopy. Finally, a significant direct correlation between HMGA1 and SAC genes expression was detected in human colon carcinomas indicating a novel mechanism by which HMGA1 contributes to cancer progression.

KEYWORDS:

CIN; HMGA1; SAC; transcriptional regulation